Evaluation of the treatment efficacy of generic enrofloxacin compared to pioneer enrofloxacin for first treatment of naturally occurring bovine respiratory disease in a commercial feedlot

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Abstract

The primary objective of this study was to compare the treatment effectiveness of generic enrofloxacin (Tenotryl™ (enrofloxacin) injectable solution; TEN) to pioneer enrofloxacin (Baytril® 100; BAY) for first treatment of naturally occurring bovine respiratory disease (BRD) on subsequent health outcomes in a commercial feedlot. Five hundred cattle identified with BRD by pen riders with rectal temperature ≥ 104.0°F (40°C) were randomized to TEN or the BAY in a 1:1 ratio within each lot. Cattle treated for BRD were returned to their home pen and monitored for 60 days to observe subsequent health outcomes. Cattle were categorized by type (dairy-beef cross or traditional beef breed). General and generalized linear mixed models were used for statistical analyses. There were no differences in first treatment success (64.29% vs 58.16%; $P = 0.19$) or case fatality risk (10.97% vs 10.65%; $P = 0.91$) comparing the TEN group to the BAY group respectively. Traditional beef breed cattle had greater body weight at time of enrollment (890.3 lb vs 749.1 lb; $P < 0.01$) and greater third treatment success (84.44% vs 41.67%; $P < 0.01$) compared to the dairy-beef cross cattle. There were no differences in health outcomes in cattle administered Tenotryl compared to Baytril 100 for first treatment of BRD in commercial feedlot cattle. From an efficacy perspective, practitioners should be able to use these products interchangeably based upon the results of the study. Additional research on general animal health outcomes of dairy-beef crosses is needed for the industry.

Key words: BRD, dairy-beef cross

Introduction

Enrofloxacin, as a single-dose therapy, is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* in beef and non-lactating dairy cattle; and for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis*. Enrofloxacin has been evaluated in both treatment[1–3] with a secondary objective of investigating the effect of disease and subsequent treatment choice on average daily gain (ADG) and metaphylaxis[4,5] and the prevalence of antimicrobial resistance (AMR) settings. Enrofloxacin is bactericidal and inhibits bacterial DNA gyrase which prevents supercoiling and replication leading to cell death.[6]

Enrofloxacin was first approved for use in cattle by the Food and Drug Administration in 1998 as the pioneer product Baytril® 100.[a,7] In 2022, a generic version of the pioneer product named Tenotryl™ (enrofloxacin) injectable solution,[b] was granted a biowaiver as the active ingredient was the same concentration and dosage form as the pioneer product and contained no inactive ingredients which may significantly affect the bioavailability of the active ingredient.[8] A blood, plasma or tissue depletion bioequivalence study was not required for the drug approval process comparing the generic to the pioneer product as the active ingredient was exactly the same formulation; however, field data comparing the generic to the pioneer product are generally necessary for adoption into production systems.

Beef sires are now commonly bred with dairy cows to create dairy-beef cross cattle marketed through the feedlot to produce high-quality carcasses,[9,10] and based on these observations, exposes future opportunities for consideration. Strip loin steaks from beef × dairy cattle can be marketed alongside conventional beef products in retail display without consumer discrimination based on color or steak shape previously experienced in steaks from straightbred dairy cattle. Additionally, beef from crossbred beef × dairy cattle cannot be discriminated against for eating quality attributes (tenderness, flavor, and juiciness). A previous study compared treatment outcomes with gamithromycin of dairy-beef cross to traditional beef breed cattle, and identified greater death loss in the dairy-beef cross cattle.[11] However, additional research and data are needed to determine appropriate management of dairy-beef crosses.

The primary objective of this study was to compare the treatment efficacy of generic enrofloxacin (Tenotryl) to pioneer enrofloxacin (Baytril 100) for first treatment of naturally occurring BRD on subsequent health outcomes in a commercial feedlot. The secondary objective was to evaluate health outcomes in dairy-beef cross cattle compared to traditional beef breed cattle along with treatment group administration.

Materials and methods

The study was performed at Hy-Plains Feedyard located near Montezuma, Kan. The feedlot was a custom cattle feeding operation. The study began August 27, 2022 and concluded January 8, 2023. All procedures were approved by the Veterinary Research and Consulting Services, LLC Institutional Animal Care and Use Committee (IACUC number 1015) prior to study initiation. The feedlot had an average population of 31,166 head during the enrollment period.

Sample size

Bovine respiratory disease case fatality risk was considered the primary outcome for the research study and used to determine sample size estimates. Baseline case fatality risk was assumed to be 10%, and ability to identify and detect for a difference of 8%. Alpha was set at 0.05, and beta set to 0.20 using a commercial software package[c] resulting in a target of 240 cattle per treatment group. Sample size was rounded up to 250 head to account for any potential removals. Sample size estimates were also developed based on the anticipation of the number of cattle eligible to enroll during the fall at the feedyard based upon historical records.

Animals

Cattle were observed daily by pen riders to identify symptoms of BRD based upon subjective evaluation which included depression/lethargy, dyspnea, abnormal respiration, sunken eyes, dehydration, nasal discharge, ocular discharge, lowered head carriage, and/or depressed ruminal fossa. All pen riders had a minimum of 3 years of experience riding pens in a commercial feedlot, and they were rotated to check different pens in the feedyard throughout the week. Any calf which displayed abnormal clinical symptoms was moved from the home pen to the hospital for confirmatory diagnosis by Veterinary Research and Consulting Services personnel and either enrolled or excluded from the study.

Inclusion criteria

Cattle were assigned a subjective clinical illness score by the personnel prior to enrollment (Table 1). Inclusion criteria for treatment study were pulled for BRD, rectal temperature ≥ 104.0°F (40°C), no previous treatments for disease, estimated > 60 days to harvest, clinical illness scores 1, 2 or 3, and absence of clinical signs of disease in other organ systems.

Lots in the commercial feedlot which did not receive a metaphylactic antimicrobial during arrival processing were eligible to be enrolled into the treatment study beginning at 1 day on feed (DOF). Lots which received a metaphylactic tulathromycin[d] at arrival processing (2.5 mg/kg of body weight (BW) subcutaneously (SC); 1.1 mL/100 lb of BW) were eligible to be enrolled 7 days after arrival processing. The decision to metaphylactically administer tulathromycin to individual lots was made by feedyard personnel based upon a subjective BRD risk classification. Risk classification was based upon origin, transportation distance, shrink, and visual appearance of the cattle upon arrival to the feedlot. Lots which received a different metaphylactic antimicrobial during initial processing were excluded from the study. Both traditional beef breed and dairy-beef-cross cattle were eligible to be included in the study.

Enrollment

Upon meeting inclusion criteria, cattle were randomized in a 1:1 ratio to 1 of 2 treatment groups within each lot: Tenotryl (TEN; 4.50 mg/lb [9.92 mg/kg] BW SC; 4.5 mL/100 lb BW SC in left neck) or Baytril 100 (BAY; 4.50 mg/lb [9.92 mg/kg] BW SC; 4.5 mL/100 lb BW SC in left neck).

An enrollment form was created to assign cattle to treatment groups within each lot. A random number generator[e] was used to create random numbers for each blank on the enrollment form. Treatment groups were written on a piece of paper and drawn out of a hat to determine the treatment group assignment based upon random numbers generated within each group of 2. The TEN treatment group was assigned to the lowest number within each pair, and the BAY treatment group was assigned to the greatest number within each pair. The first calf which met the case definition was assigned to the treatment group assigned to the first blank on the enrollment form. The next calf from the same lot which met the case definition was assigned to the second blank on the enrollment form for the pair. When a new eligible BRD pull was enrolled from a different lot in the feedlot, the calf was assigned to start a new group of 2. Treatments of cattle were randomized in an effort to evenly distribute treatments within lot.

A single ear tag, cross-referenced to the feedlot lot tag, was used to identify each calf upon study enrollment for duplicate identification. The date the calf was eligible to be re-treated was written on the tag for the pen rider to be able to identify when it was eligible for additional treatment if needed. A 3-day post-treatment interval (PTI) was used for both the TEN and BAY treatment group. Individual body weight and rectal temperature were recorded for all cattle enrolled and recorded in a feedlot animal health computer system.[f] Cattle treated for BRD were returned to their home pen. Cattle were monitored for 60 days, well beyond the 28 day-withdraw period,[b] to observe for subsequent health outcomes by feedlot pen riders blinded to treatment group. Feedlot treatment and pen riders were different personnel.

Table 1: Description of clinical illness scoring system used to assess cattle upon study enrollment into a study comparing generic enrofloxacin to pioneer enrofloxacin for first treatment of bovine respiratory disease.

Clinical illness score	Criteria
0	Normal; bright; alert; responsive
1	Mild depression; signs of weakness usually not present; responsive
2	Moderate depression; some signs of weakness; may be reluctant to stand
3	Severe depression; difficulty standing; head lowered or extended
4	Moribund; unable to stand; mouth breathing

BRD retreatments

Cattle were eligible for retreatment if identified by pen riders with recurrent BRD and met or exceeded the PTI period. Retreatment eligibility also included a rectal temperature ≥ 104.0°F (≥ 40°C) or lost body weight from first treatment. Cattle which displayed a clinical illness score ≥ 3 were re-treated regardless of rectal temperature or body weight change if exceeded the PTI period. Cattle which required a second treatment for BRD were administered florfenicol[g] (40 mg/kg of BW SC; 6 mL/100 lb BW). A 3-day PTI was used after the second treatment for BRD. Cattle requiring a third treatment for BRD were administered oxytetracycline[h] (19.8 mg/kg of BW SC; 4.5 ml/100 lb BW). No cattle were marketed during the 60-day monitoring period.

Gross necropsies

A gross necropsy was performed by a veterinarian or trained feedlot personnel on all enrolled animals which died during the study. A cause of death was determined for each case that died during the monitoring period based upon gross pathological lesions. No diagnostic samples were collected.

Feed, housing and water

Cattle were fed diets formulated to meet or exceed National Research Council[12] the National Research Council (NRC maintenance requirements. Feed rations consisted of steam-flaked corn, wet distillers' grains, ground alfalfa hay, supplement and ground prairie hay. No feed-grade antimicrobials for control or treatment of BRD were fed to cattle throughout the trial. Cattle were housed in dirt floor pens consistent with commercial feedlot operations in the area. Water was provided ad libitum through an automatic float-activated system.

Data management

Data management steps were completed in a spreadsheet.[e] Data were removed prior to analysis on cattle which died due to causes other than BRD, required antimicrobial treatments not related to BRD, or were treated with a different treatment regimen to manage drug withdrawal periods. Binary variables were created for treatment success and BRD case fatality risk. Treatment success was defined as not requiring additional treatment for BRD and not dying during the 60-day monitoring period. Case fatality risk was defined as cattle dying due to BRD during the 60-day monitoring period. Treatment death interval was calculated from the day of first treatment for BRD to the day of death for cattle that died of BRD during the monitoring period. Cattle type (dairy-beef-cross or traditional beef breed cattle) were categorized at the lot level as no mixed cattle type lots were present in the feedlot.

Statistical analyses

Data were imported into a commercial software package[c] for analyses. Data analyses were aligned with the randomized complete block design with individual animal as the experimental unit. Generalized linear mixed models were used for statistical analyses with distributions and standard link functions aligned with the outcome variable. Gaussian distribution was used for continuous outcomes (DOF, BW and enrollment rectal temperature), binomial was used for dichotomous outcomes (treatment success and case fatality risk), and cumulative logistic was used for ordinal outcomes (sex, clinical illness score and cattle type). Lot was included as a random intercept term in animal-level models to account for clustering within lots. Secondary analyses of interaction with treatment group and cattle type were performed. Differences exhibiting a P value ≤ 0.05 were considered statistically significant.

Results

A total of 500 cattle were enrolled into the treatment study (TEN n = 250; BAY n = 250). Enrollments averaged 6.67 cattle/day (median 5, range 0 to 30). A total of 7 cattle were removed prior to analysis (TEN n = 5; BAY n = 2) due to death by hardware disease (TEN n = 1), death due to digestive issues (TEN n = 2), death due to congestive heart failure (TEN n = 1), treated with different antimicrobial at 57 days after initial treatment to manage a shorter withdrawal time (TEN n = 1), and treated with oxytetracycline for foot rot and diphtheria (BAY n = 2). These removals occurred prior to the end of the 60-day monitoring period leaving 493 total cattle available for analyses (TEN n = 245; BAY n = 248). None of the removals appeared to be in relation to treatment group administration. Four hundred thirty-seven cattle were not administered a metaphylactic antimicrobial on arrival, and 56 cattle were administered tulathromycin upon arrival processing. Three hundred fifty-two were traditional beef breed cattle and 141 cattle were dairy-beef cross.

There were no significant differences ($P > 0.05$) in enrollment characteristics (Table 2) or clinical health outcomes (Table 3) by treatment group. There were no statistical differences in first treatment success (64.29% vs 58.16%; $P = 0.19$) or case fatality risk (10.97% vs 10.65%; $P = 0.91$) comparing the TEN group to the BAY group respectively (Figure 1). There were statistically significant interactions between treatment group and cattle-type ($P > 0.05$; Table 4). Traditional beef breed cattle had greater body weight at time of enrollment ($P < 0.01$) and greater third treatment success ($P < 0.01$) compared to the dairy-beef-cross cattle (Table 4).

Discussion

To the authors' knowledge, this is the first published research comparing a generic formulation of enrofloxacin to the pioneer product. Treatment success and case fatality risk of enrofloxacin products in the current study are similar to previously reported studies evaluating treatment efficacy of enrofloxacin in low-risk populations.[2,3] also known as bovine respiratory disease (BRD). Research studies which used enrofloxacin as the first treatment for BRD after metaphylaxis in high-risk populations resulted in poorer treatment outcomes compared to the current study;[13,14] however, the low-risk populations represented in this study are a greater proportion of the feedlot industry.[15]

Tenotryl was provided a biowaiver by the Food and Drug Administration since the active ingredient was the same concentration and dosage form as the pioneer product, and the antimicrobial contains no inactive ingredients which may significantly affect the bioavailability of the active ingredient. A bioequivalent study was not required to be conducted as part of the drug approval process; however, the decision was made to evaluate efficacy for clinical outcomes in the field. Results of this study found no statistically significant differences in health outcomes comparing the generic product to the pioneer product. There are limited published studies comparing generic products to pioneer products for antimicrobials in cattle. Internal studies have been performed, but typically are not submitted for peer-review publication. There are a few studies which have

Table 2: Characteristics of cattle at enrollment into treatment groups. *P*-value displayed is main effect of treatment group. Model included random effect for lot for continuous outcomes.

Outcome	TEN[1]			BAY[2]			*P*-value
Number of observations, n	245		-	248			_
Days on feed at enrollment, d	58.74	±	2.87	58.40	±	2.86	0.76
Enrollment body weight, lb	864.6	±	17.26	858.6	±	17.17	0.48
Enrollment rectal temperature, °F	104.9	±	0.06	105.0	±	0.06	0.34
Sex							
Steer	70.20	±	2.92	72.17	±	2.84	0.63
Heifer	29.80	±	2.92	27.82	±	2.84	
Clinical illness scores							
1	41.56	±	3.76	44.75	±	3.74	
2	54.90	±	3.53	52.14	±	3.51	0.49
3	3.54	±	0.93	3.12	±	0.83	
Metaphylaxis status							
None	88.57	±	2.03	88.71	±	2.01	0.96
Tulathromycin	11.43	±	2.03	11.29	±	2.01	
Cattle type							
Traditional beef breed, %	71.84	±	2.87	70.97	±	2.88	0.83
Dairy-beef, %	28.16	±	2.87	29.03	±	2.88	

1 Tenotryl™, Virbac Corporation, Westlake, TX

2 Baytril® 100, Elanco Animal Health, Greenfield, IN

Table 3: Model-adjusted least square means (± standard error) of health outcomes for first treatment of bovine respiratory disease by treatment group. From generalized linear mixed models with a random intercept to account for clustering within lots.

Outcome	TEN[1]			BAY[2]			*P*-value
First treatment success,[3] %	64.29	±	3.92	58.16	±	4.00	0.19
BRD second treatment, %	28.13	±	3.31	35.22	±	3.51	0.10
Second treatment success,[3] %	51.39	±	5.89	56.67	±	5.22	0.50
BRD third treatment, %	9.94	±	2.56	10.16	±	2.59	0.93
Third treatment success,[3,4] %	75.00	±	8.18	75.86	±	7.94	0.94
BRD case fatality risk, %	10.97	±	2.66	10.65	±	2.62	0.91
Treatment death interval, d	12.80	±	2.54	18.43	±	2.48	0.11

1 Tenotryl™, Virbac Corporation, Westlake, TX

2 Baytril® 100, Elanco Animal Health, Greenfield, IN

3 Treatment success defined as not requiring additional treatment for BRD and not dying within the 60-day monitoring period due to BRD.

Figure 1: Outcome means (± standard error) by treatment group (TEN-blue bars, Tenotryl™ [Virbac Corporation]; BAY-red bars, Baytril® 100 [Elanco Animal Health]) from generalized linear mixed models with a random intercept to account for clustering within lots. First bovine respiratory disease treatment success and case fatality risk were not different between treatment groups (P = 0.19 and P = 0.91, respectively).

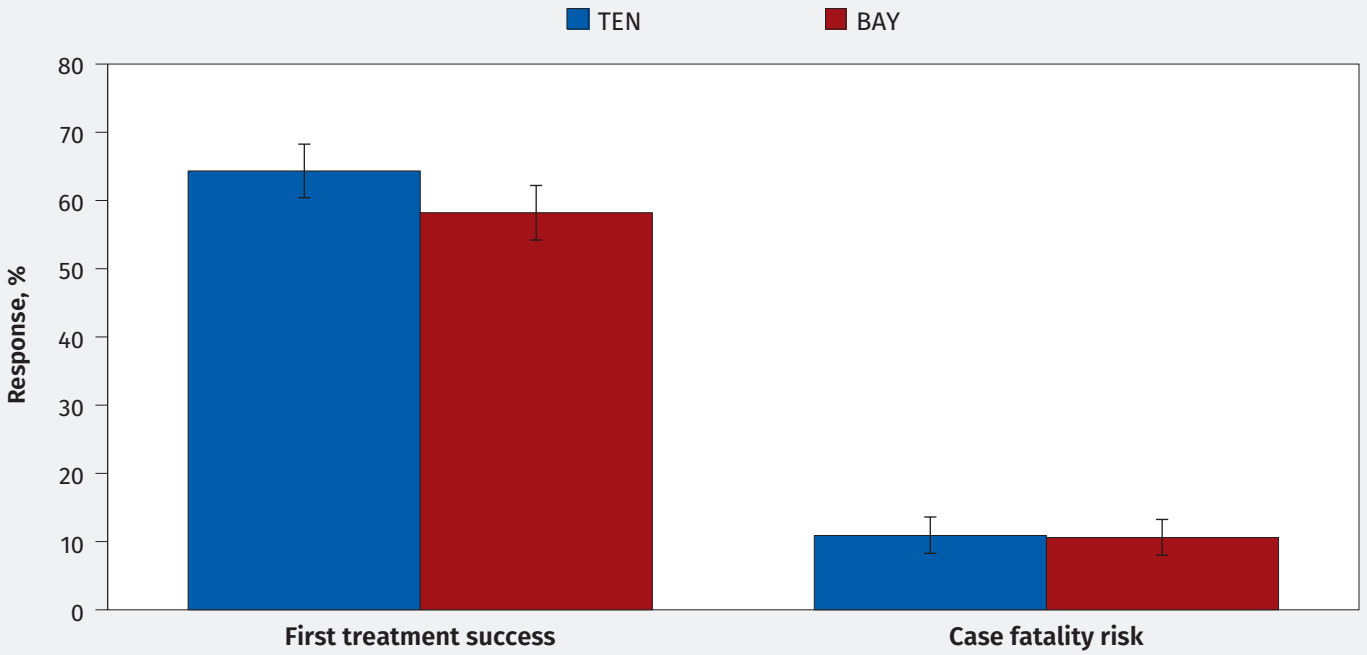

Table 4: Model-adjusted least square means (± standard error) of health outcomes for first treatment of bovine respiratory disease by cattle type from generalized linear mixed models with a random intercept to account for clustering within lots.

Parameter	Dairy-beef cross			Traditional beef breed			Dairy-beef / traditional beef breed *P*-value	Treatment x cattle type interaction *P*-value*
Number of observations, n	141			352			–	–
Days on feed at enrollment, d	57.59	±	6.23	58.82	±	3.16	0.86	0.88
Enrollment body weight, lb	749.1	±	35.22	890.3	±	18.01	< 0.01	0.53
Enrollment rectal temperature, °F	104.97	±	0.10	104.96	±	0.06	0.93	0.18
Clinical illness scores								
1	45.04	±	5.71	42.55	±	3.42		
2	51.87	±	5.17	54.04	±	3.26	0.70	0.75
3	3.09	±	0.98	3.41	±	0.87		
First treatment success,[1] %	59.18	±	6.35	61.84	±	3.69	0.71	0.94
BRD second treatment, %	32.76	±	5.08	31.35	±	3.08	0.81	0.90
Second treatment success,[1] %	65.96	±	6.91	49.57	±	4.66	0.06	0.81
BRD third treatment, %	7.26	±	2.67	11.45	±	2.49	0.19	0.59
Third treatment success,[1] %	41.67	±	14.23	84.44	±	5.40	< 0.01	0.91
BRD case fatality risk, %	13.01	±	4.13	10.07	±	2.42	0.48	0.83
Treatment death interval, d	18.66	±	3.29	14.42	±	2.26	0.30	0.14

1 Treatment success defined as not requiring additional treatment for BRD and not dying within the 60-day monitoring period due to BRD.

compared the efficacy of generic parasiticides compared to pioneer.[16,17] More reporting and publishing of studies are needed for the beef industry to make more informed decisions for management, treatment and processing recommendations.

Comparing the results from the dairy-beef cross to the traditional beef breed cattle provides some novel results. There were no significant treatment group by cattle type interactions identified, indicating the magnitude of difference in response was not different between cattle types for both enrofloxacin products. These findings suggest practitioners can utilize Tenotryl or Baytril 100 interchangeably in traditional beef breed or dairy-beef cattle. The only significant difference found between cattle types was a poorer third treatment success in the dairy-beef compared to the traditional beef breed cattle ($P < 0.01$); however, second treatment success tended to be greater for the dairy-beef compared to the traditional beef breed cattle ($P = 0.06$). One potential reason for this difference may be cattle were monitored for 60 days from initial treatment since first treatment was the primary objective of the study. Second and third treatments may have had subsequent different lengths of monitoring depending on when they occurred during the initial 60-day monitoring period. A previous treatment study evaluated the health outcomes of dairy-beef compared to traditional beef breed cattle and observed poorer third treatment success and case fatality risk in the dairy-beef cattle.[11] It is important to note the dairy-beef cattle were 242.2 lb (109.9 kg) lighter BW at time of study enrollment compared to the traditional beef breed cattle in the previous study.[11] The dairy-beef cattle in the current study were 141.2 lb (64.0 kg) lighter BW than the traditional beef breed cattle for the current study. The study was not designed to determine if the improvement of the treatment outcomes were due to the differences in the antimicrobial products evaluated or differences in BW. Body weight had been associated with treatment response.[18,19] Another hypothesis for the differences in health outcomes between cattle type may be due to the rearing environment and previous exposure to antimicrobials at the calf ranch. More research is needed in the dairy-beef-cross population for the feedlot industry to develop appropriate antimicrobial protocols.

Limitations of this study were the monitoring of the cattle only occurred for 60 days post-enrollment, and sample size based on an 8% difference in case fatality risk difference between the two treatment groups. The 60-day post-enrollment monitoring period had been used in studies previously,[11,20] and is longer than the 35-day monitoring period as previously suggested in other BRD treatment studies.[21] The authors designed and analyzed the study to evaluate if there were clinical differences between the treatment groups rather than evaluating equivalence within a certain delta value. Clinically there appeared to be minimal differences between the treatment groups.

Conclusions

There were no statistically significant differences in health outcomes in cattle which were administered Tenotryl compared to Baytril 100 for first treatment of BRD in commercial feedlot cattle. Practitioners should be able to use these products interchangeably as the FDA approved the generic product as bioequivalent, and the study reported here found no statistically significant differences between generic and pioneer enrofloxacin in case fatality risk and other outcomes. Additional research on animal health outcomes of dairy-beef crosses is needed for the beef industry.

Endnotes

[a]Baytril® 100, Elanco Animal Health, Greenfield, IN

[b]Tenotryl™ (enrofloxacin) injectable solution, Virbac Corporation, Westlake, TX

[c]R Studio Team 2022, Boston, MA

[d]Tulissin® 100 (tulathromycin injection) injectable solution, Virbac Corporation, Westlake, TX

[e]Microsoft Office Excel, Microsoft Corp, Redman, WA

[f]Animal Management System, Animal Health International, Greeley, CO

[g]Nuflor®, Merck Animal Health, Whitehouse Station, NJ

[h]Biomycin® 200, Boehringer Ingelheim Animal Health USA, Inc., Duluth, GA

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Conflict of interest statement

Drs. Jessica Newberry and Fabrice Payot are employees of Virbac Corporation; however, neither were directly involved in conducting the study. Drs. Miles Theurer and J. Trent Fox have had previous research or consulting paid by Elanco Animal Health.

Author contributions

All authors were involved in conception and study design. Dr. Miles Theurer was involved in study data acquisition and analyses. All authors were involved with manuscript drafting and/or revising process. All authors have approved the final version of this manuscript for publication.

Abbreviations

BAY	Baytril® 100
BRD	Bovine respiratory disease
BW	Body weight
DOF	Days-on-feed
PTI	Post-treatment interval
SC	Subcutaneous
TEN	Tenotryl™

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